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A Mechanistic Investigation of the Autoxidation of Alkylpyrroles

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The initial stages of the autoxidation of 1,2,3,4-Tetrahydrocarbazole in the presence of trace amounts of iron(III) is proposed to involve a non free radical chain mechanism. This mechanism has been designed as electron transfer initiated oxidation (ETIO). The characteristics of this reaction are discussed.

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Iron (III) Initiated Autoxidation of 1,2,3,4-Tetrahydrocarbazole: An Example of Electron Transfer Initiated Autoxidation.

Summary: The initial stages of the autoxidation of 1,2,3,4-Tetrahydrocarbazole in the presence of trace amounts of iron (III) is proposed to involve a non free radical chain mechanism.

Sir: The significance of the reactions of biomolecules with molecular oxygen derived free radicals (i.e. active oxygen) is becoming increasingly apparent in the fields of biochemistry[1] and medicine.[2] Oxygen derived free radicals have been implicated in aging, cerebrovascular damage, atherosclerosis, ischemic-reperfusion injury, and cancer.[3] Recently, evidence has been presented that suggests that increased body iron stores are associated with an increased risk of cancer.[4]

Certain transition metal ions are known to catalyze the autoxidation of various organic compounds. Under acidic conditions, metal ion catalyzed decomposition of trace organic hydroperoxides has been suggested as a source of free radicals which initiate radical chain autoxidation[5] (eq. 1-2).

$$M^{n+} + ROOH \longrightarrow M^{(n-1)+} + R\text{-}O\cdot + OH^- \qquad (1)$$

$$R\text{-}O\cdot + R\text{-}H \xrightarrow{O_2} R\text{-}OH + R\text{-}O_2\cdot \longrightarrow \text{ect.} \qquad (2)$$

Recently it has been suggested that the reduction of hydrogen peroxide by iron complexes in neutral solution

per CG

results in the formation of either high oxidation state iron-oxo species (i.e. ferryl ion)[6] or the "caged" hydroxyl radical.[7] In autoxidations, the source of the primordial hydroperoxide has been an enigma, owing to the inherent difficulty of experimental observation of the primary initiation process.[8]

However, several mechanisms have been proposed for direct reaction of organic substrates with molecular oxygen. For instance, Carlsson and Robb have reported spectral and kinetic evidence that suggests the liquid phase autoxidation of tetralin involves rate determining reduction of oxygen to form H_2O_2 and free radicals[8] (eq. 3).

$$RH + O_2 + RH \rightleftharpoons [RH\cdots O_2] + RH \rightleftharpoons 2R\cdot + H_2O_2 \qquad (3)$$

Recently Correa, Hardy, and Riley have proposed that the selective autoxidation of various electron-rich substrates (tertiary amines, mercaptans, olefins, and alkynes) under elevated oxygen pressures (>20 burs) and temperatures (>90° C) involves rate determining electron transfer from the substrate to oxygen[9] (eq. 4-6).

$$Sub + O_2 \rightleftharpoons Sub\cdot^+ + O_2^- \qquad (4)$$

$$Sub\cdot^+ + O_2 \rightleftharpoons Sub\text{--}O\text{--}O\cdot \qquad (5)$$

$$Sub\text{--}O\text{--}O\cdot + Sub \rightleftharpoons Sub\text{--}O\text{--}O^- + Sub\cdot^+ \qquad (6)$$

Riley, Smith, and Correa have reported that the autoxidation of thioethers to sulfoxides is catalyzed by Ce(IV) and have proposed that an oxygen driven Ce(IV)/Ce(III) redox cycle gives rise to the catalysis[10] (eq. 7-10).

$$R_2S + Ce^{4+} \text{------} > R_2S\cdot^+ + Ce^{3+} \qquad (7)$$

$$R_2S^{\cdot+} + O_2 \longrightarrow R_2S{-}{-}O{-}{-}O. \quad (8)$$

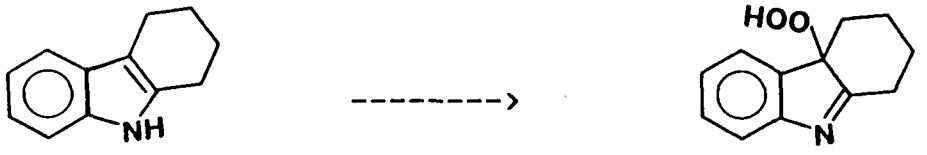
$$R_2S{-}{-}O{-}{-}O. + Ce^{3+} \longrightarrow R_2S{-}{-}O{-}{-}O^- + Ce^{4+} \quad (9)$$

$$R_2S{-}{-}O{-}{-}O^- + R_2S \longrightarrow 2\ R_2S{-}{-}O^- \quad (10)$$

We have proposed that autoxidations in which the rate determining step involves electron transfer from the organic substrate to molecular oxygen be designated as electron transfer initiated autoxidations[11] (ETIA).

We propose that certain transition metal ions are capable of catalyzing the ETIA pathway.[12]

We wish to report experimental evidence for the operation of an ETIA mechanism for the iron (III) initiated autoxidation of 1,2,3,4-tetrahydrocarbazole (THC). Beer, McGrath, and Robertson have reported that when warm solutions (ethyl acetate/hexane) of tetrahydrocarbazole are allowed to stand overnight, a good yield of the corresponding crystalline 3- hydroperoxyindolenine (A) can be isolated[13] (eq. 11). In addition, a free radical chain mechanism has been proposed for the formation of A.



(11)

(A)

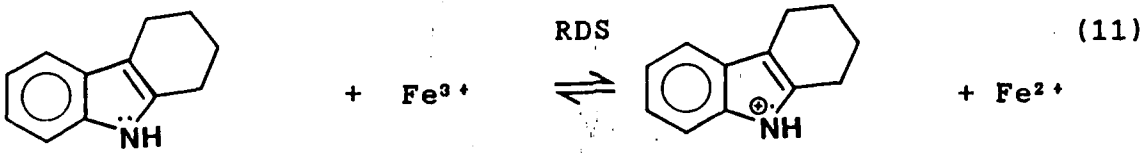
Figure 1 reveals the reaction profile for 3-hydroxyperoxy-indolenine (A) formation (in ethyl acetate/hexane) (determined by iodometric titration), as a function of time, in the presence of a trace amount of iron (III) acetylacetonate (acac). The presence of iron (III) (acac)

results in a tremendous shortening of the induction period (as compared with the un-initiated autoxidation) and a reaction profile that reveals two distinct phases of hydroperoxide formation. The initial phase (phase I) (indicated by arrows in Fig. 6) reveals a slow cyclic hydroperoxide production while later the profile changes into a more rapid, relatively linear phase (phase II) of hydroperoxide formation. When the same iron (III) (acac) initiated autoxidation is preformed in the presence of a large concentration (i.e. five equivalents based on THC) of a highly efficient radical scavenger (Vitamin E),[14] phase II hydroperoxide formation is supressed while phase I hydroperoxide formation continues. A plot of ln[THC] (determined by GC) vs. time for the Fe(III) (acac) initiated autoxidation, in the presence of 1 equivalent of Vitamin E, reveals a pseudo-first order rate of 1.66×10^{-6} sec^{-1} (r= .999) for Phase I (Fig 2).

The observed phase I hydroperoxide formation in the presence of Vitamin E is either produced via a non-free radical chain mechanism or is due to operation of a "short" radical chain pathway (or "caged" hydroxyl radical; ferryl ion) initiated by iron catalyzed decomposition of primordial hydroperoxide. In order to test the latter hypothesis the following experiment was run. The pseudo forst order rate constant for the iron (III) (acac) catalyzed decomposition of a purified solution of the 3-hydroperoxyindolenine (A) in the presence of excess O_2 and five equivalents of Vitamin E

identical experiment in which one equivalent of purified tetrahydrocarbazole was also added (Fig 3). The fact that within our experimental error the two experiments yielded the same rate constant for hydroperoxide decomposition suggests that if radical initiators are produced during hydroperoxide decomposition, the experimental concentration of Vitamin E used in our experiments is sufficient to sequester radical initiated autoxidation.

Therefore, we propose that the phase I behavior observed during the iron (III) initiated autoxidation of 1,2,3,4-tetrahydrocarbazole is an example of metal ion catalyzed electron transfer initiated autoxidation (ETIA). We propose a mechanism for the Phase I Fe (III) initiated autoxidation of tetrahydrocarbazole (eq. 11-14) similar to that proposed by Riley et al.[10] for Ce (IV) catalyzed sulfoxide formation.



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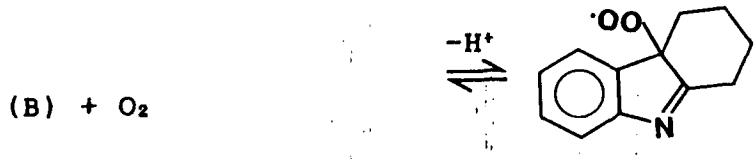

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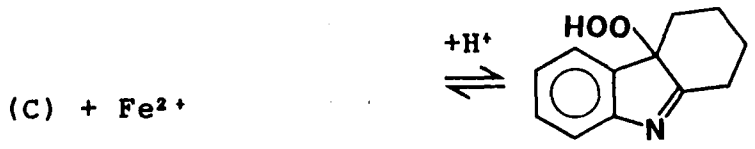

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The rate of hydroperoxide formation by this pathway is slightly greater than the simultaneous iron catalyzed hydroperoxide decomposition.

Work is in progress in our laboratory to further define ETIA and characterize other examples of this mechanism in autoxidation.

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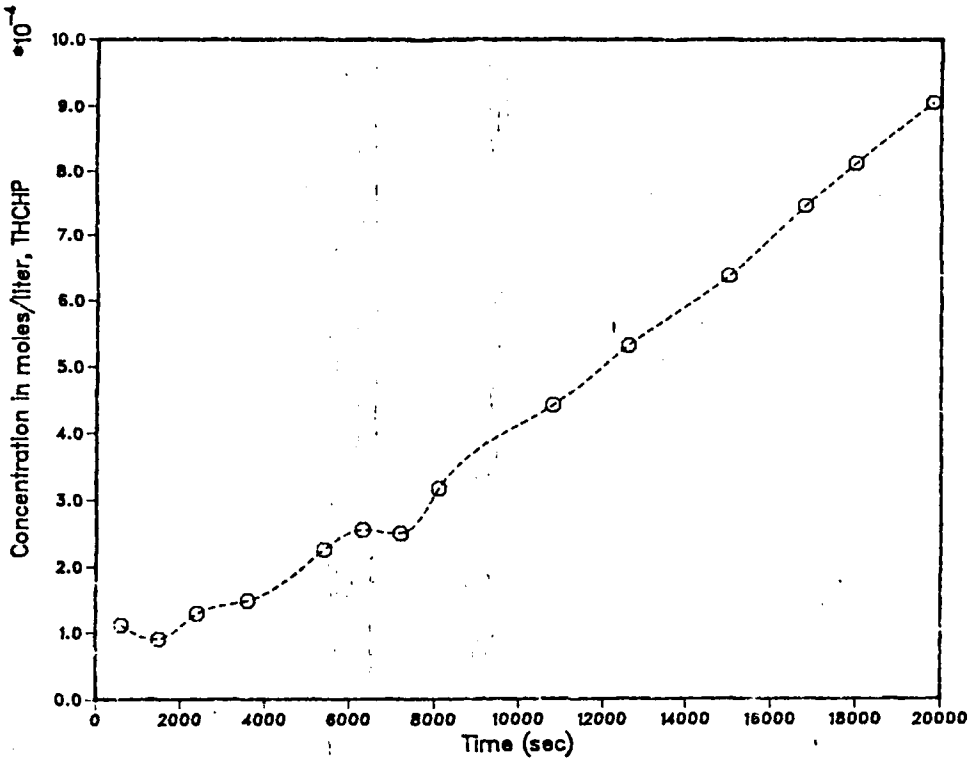
Figure 1a. Autoxidation of tetrahydrocarbazole in the presence of Fe(III)(acac)(10 mg) in 1:1 EtOAc/hexane at 40° C.

Figure 1b. "Phase I" (indicated by arrows) autoxidation of tetrahydrocarbazole in the presence of Fe(III)(acac)(10 mg) in 1:1 EtOAc/hexane at 40° C.

a.


*10^-4
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Concentration in moles/liter, THCHP
0
2000
4000
6000
8000
10000
12000
14000
16000
18000
20000
Time (sec)

b.

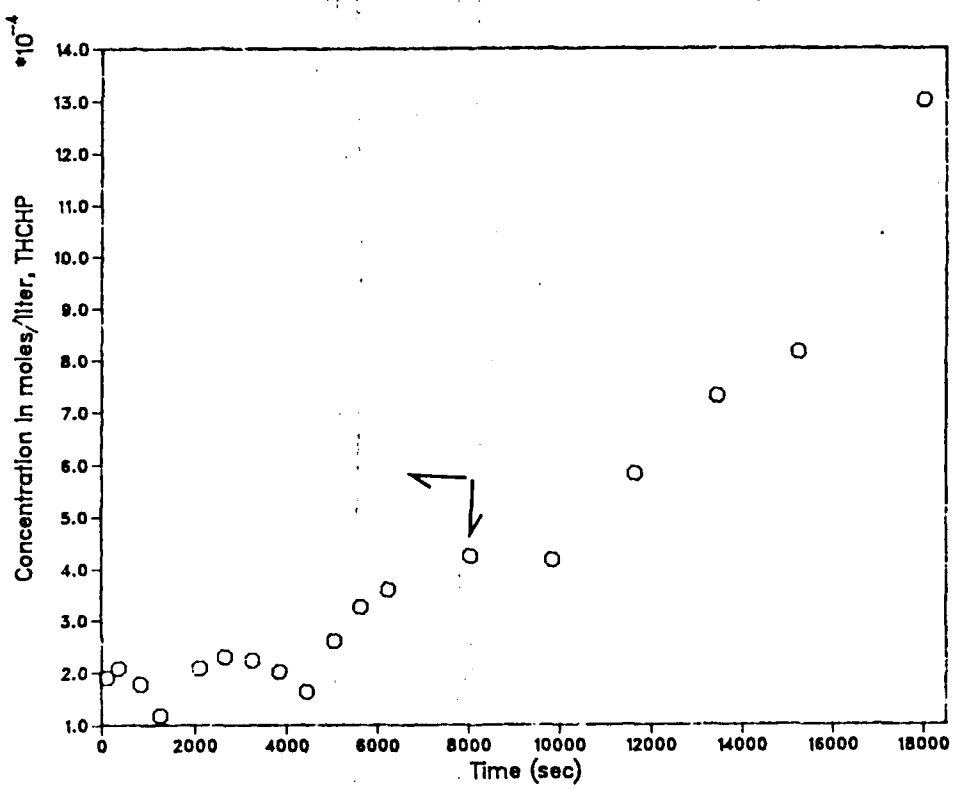

*10^-4
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
Concentration in moles/liter, THCHP
0
2000
4000
6000
8000
10000
12000
14000
16000
18000
Time (sec)

Figure 2. Pseudo-first order rate constant for the autoxidation of tetrahydrocarbazole in the presence of Fe(III)(acac)(10 mg) and 1 equivalent of Vitamin E in 1:1 EtOAc/hexane at 50°C ($k = 1.66 \times 10^{-6}$ sec^{-1}; $r = .999$).

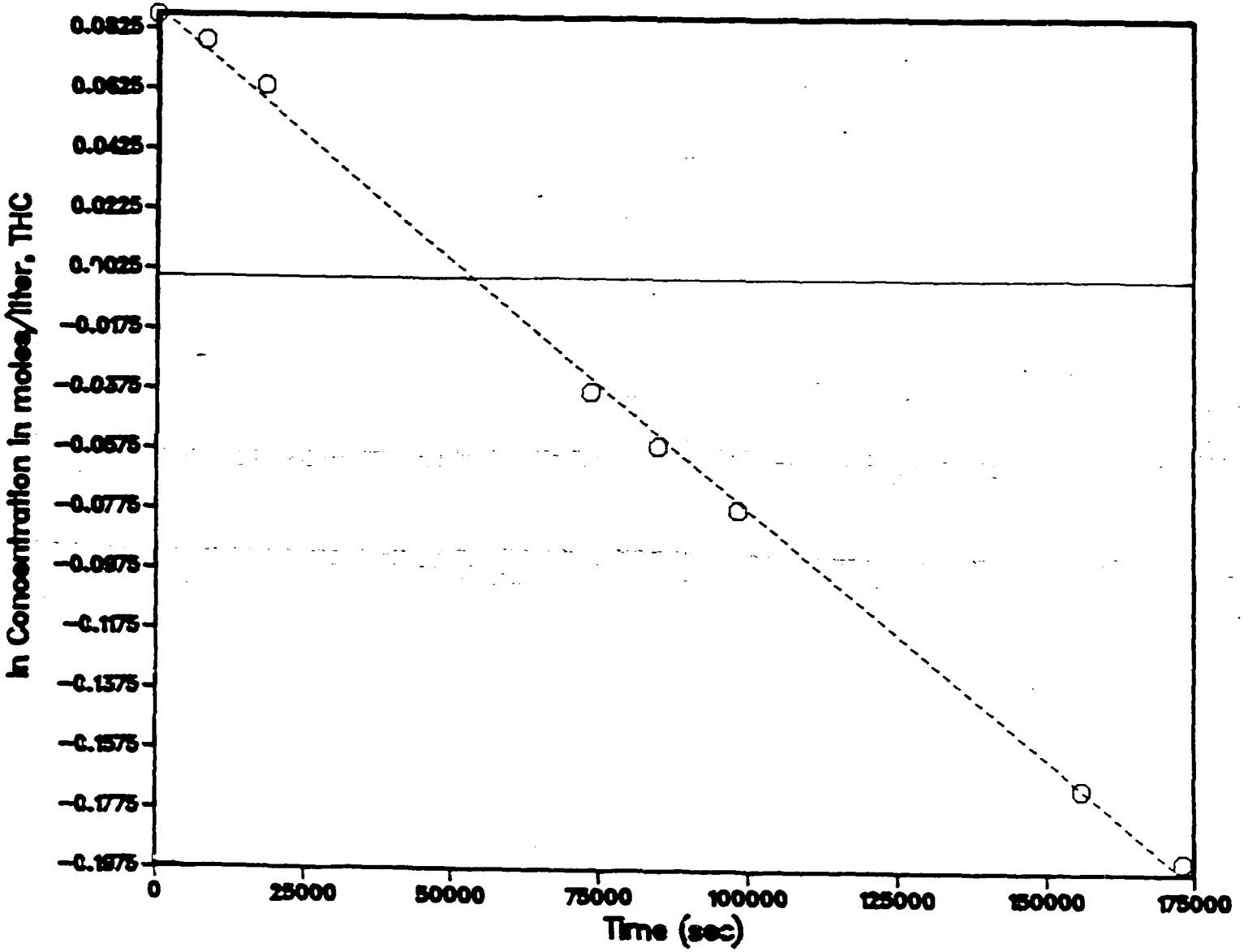
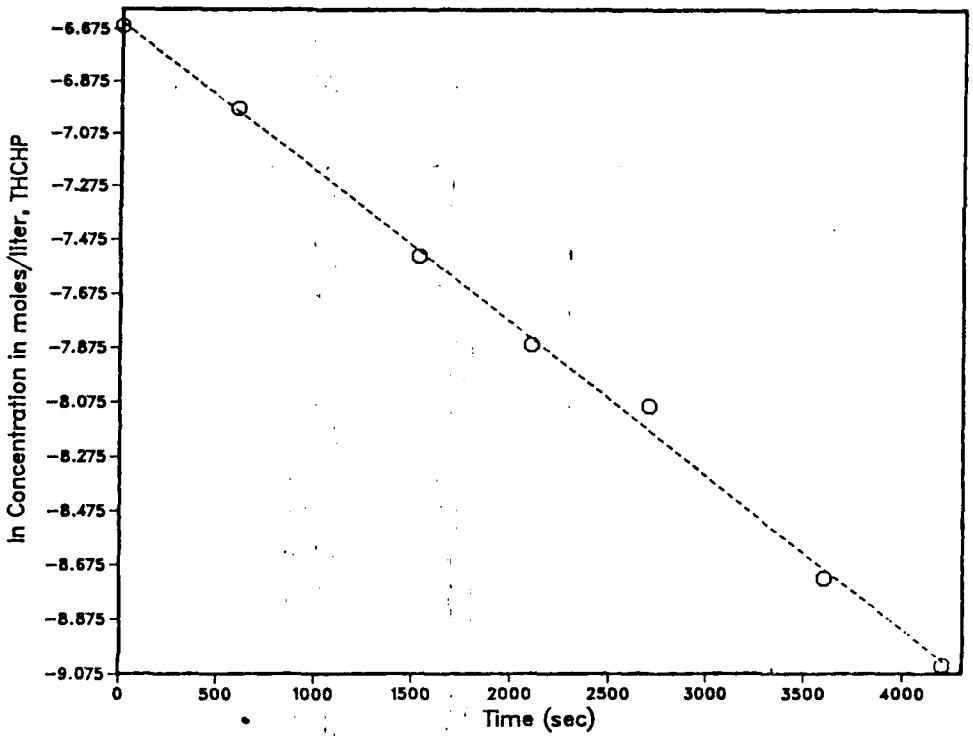

0.0825
0.0625
0.0425
0.0225
0.1025
-0.0175
-0.0375
-0.0575
-0.0775
-0.0975
-0.1175
-0.1375
-0.1575
-0.1775
-0.1975
ln Concentration in moles/liter, THC
0
25000
50000
75000
100000
125000
150000
175000
Time (sec)

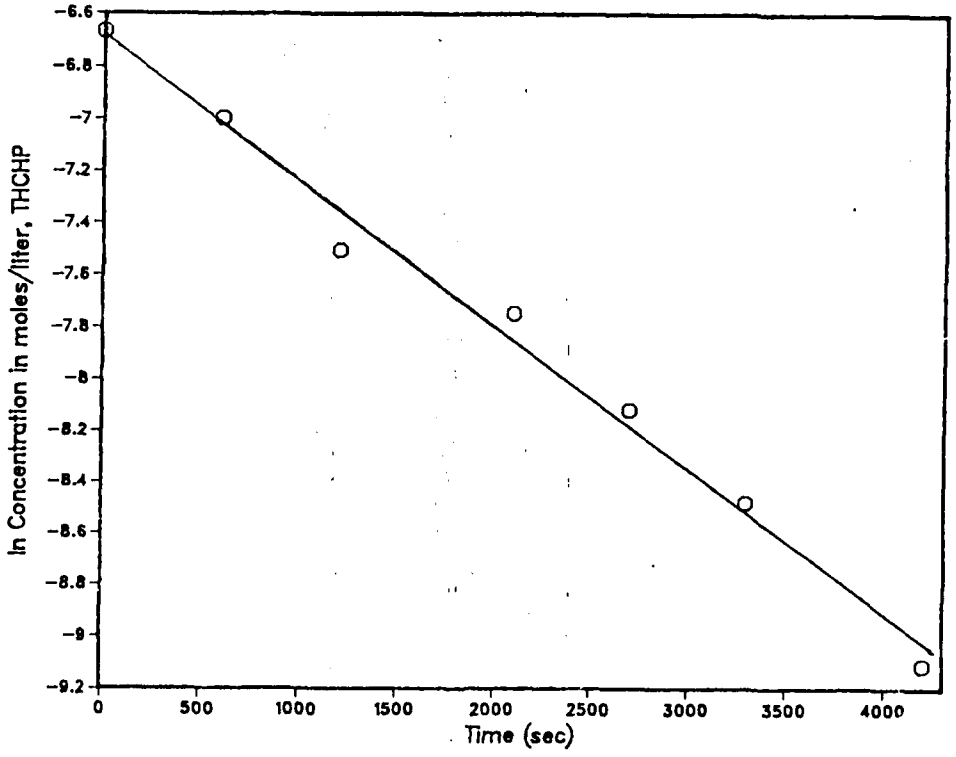
Figure 3a. Pseudo-first order rate constant for the decomposition of tetrahydrocarbazolehydroperoxide in the presence of Fe(III)(acac)(10 mg), excess oxygen, and 5 equivalents of Vitamin E in EtOAc/hexane (1:1) at 40°C ($k = -5.67 \times 10^{-4}$ sec^{-1}; $r = .999$).

Figure 3b. Same experimental conditions as above with 1 equivalent of tetrahydrocarbazole added ($k = -5.58 \times 10-4$ sec^{-1} $r = .994$).

a.


ln Concentration in moles/liter, THCHP
-6.675
-6.875
-7.075
-7.275
-7.475
-7.675
-7.875
-8.075
-8.275
-8.475
-8.675
-8.875
-9.075
0
500
1000
1500
2000
2500
3000
3500
4000
Time (sec)

b.


ln Concentration in moles/liter, THCHP
-6.6
-6.8
-7
-7.2
-7.4
-7.6
-7.8
-8
-8.2
-8.4
-8.6
-8.8
-9
-9.2
0
500
1000
1500
2000
2500
3000
3500
4000
Time (sec)